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Patients with Rheumatoid Arthritis Benefit from Early 2nd Line Therapy: 5 Year Followup of a Prospective Double Blind Placebo Controlled Study

CHARLOTTE EGSMOSE, BIRGER LUND, GUNILLA BORG, HOLGER PETTERSSON, ELISABETH BERG, ULF BRODIN, and LUDVIG TRANG

ABSTRACT. ***Objective.*** To compare 2 treatment strategies in a prospective 5 year study of patients with rheumatoid arthritis (RA): early treatment with slow acting antirheumatic drugs (SAARD) versus a "wait and see" attitude.

Methods. One hundred thirty-seven patients with RA of <2 years' duration entered a double blind placebo controlled study: patients in the "early" (E) group were treated with auranofin within one year of diagnosis of RA, and SAARD treatment in the initially placebo treated group was delayed 8 months compared with the former group. [The results after 2 years clearly favored early treatment (Borg G, Allander E, Lund B, *et al*: *J Rheumatol 1988;*15:1747–54)].

Results. After a total observation period of 5 years in 75 representative patients, continued improvement in the E group was demonstrated, and differences between the 2 groups were maintained with regard to clinical variables, outcome measures, and radiographic evaluation.

Conclusion. The results indicate the existence of a therapeutic window in RA within the first 2 years of the disease. **(*J Rheumatol 1995;*22:2208–13)**

Key Indexing Terms:
RHEUMATOID ARTHRITIS SAARD AURANOFIN THERAPEUTIC WINDOW
FIVE YEAR PROSPECTIVE STUDY OUTCOME MEASURES

Prospective studies in rheumatoid arthritis (RA) investigating the effect of medical intervention on outcome in patients followed for more than 2 years are scarce. Conflicting results have been reported in the few studies performed. Scott, *et al*[1] found indications for an improvement with less radiographic change during the first decade of the disease, but a considerable decline in functional capacity between 10 and 20 years of disease. Other studies with roughly the same period of observation conclude that RA is becoming a less severe disease, at least with regard to radiological outcome[2,3]. This improvement is ascribed to the development of better therapeutic modalities and to the use of slow acting antirheumatic drugs (SAARD) at an earlier stage.

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The beneficial effect of early initiation of treatment is supported by the work of Wolfe, *et al*[4], who followed over 500 patients with variable disease duration (from less than 2 years to more than 20 years) for over 5 years. A striking and statistically significant improvement in all variables was observed in the patient group seen within 2 years of disease onset and followed for an additional 2 years. This was in contrast to all the other patient groups with a longer disease duration, in whom functional loss was found to increase over time in spite of treatment. The authors speculate that, relatively early, with a disease duration of less than 2 years, a therapeutic window exists in which the patients are more responsive to treatment.

When during the first 2 years of RA does this therapeutic window appear? To answer this question, a 2 year double blind placebo controlled clinical trial was carried out in patients with RA of less than 2 years duration. "Early" start with auranofin, i.e., as soon as possible after diagnosis, was compared to a "wait and see" attitude, i.e., starting SAARD treatment after clinical deterioration.

Results at 2 years for outcome and process variables, including radiographic data, have been reported[5]. We describe an additional 3 years' followup in 75 of these patients, a representative subset of the patients included in the original study.

The results indicate that the therapeutic window appears early, less than 2 years after the start of the disease. The time span between initiation of SAARD therapy in the 2

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groups identifies a therapeutic opportunity with regard to development of radiographic changes and process and outcome measures after 5 years.

MATERIALS AND METHODS

Study design and patients. The treatment schedule and an overview of SAARD therapy given in the 2 groups is presented in Figure 1. The study sample and the design of the original 2 year study were as published[5]. A brief summary follows.

Study sample and study design up to 2 years: 137 patients with active definite or classical RA (ARA criteria[6]), disease duration 2 years or less, were included in a double blind placebo controlled trial. No patient had previously been treated with 2nd line drugs. Patients were randomly allocated to one of 2 treatment strategies: "early" treatment with auranofin (Group E) or delayed treatment with other SAARD (Group D). Patients in Group E received auranofin 6 mg daily and Group D identical placebo tablets. All patients received concomitant nonsteroidal antiinflammatory drugs (NSAID). Analgesics and local steroid injections were given if needed, and joint surgery was permitted. Patients were withdrawn from the double blind medication in case of insufficient therapeutic efficacy (after 4 months at the earliest) and/or intolerable side effects (at any time point). These patients were subsequently switched to open SAARD treatment, primarily D-penicillamine or antimalarial drugs, but they remained in the study and were included in the final analysis (intent to treat) as failures.

The patients were seen by the treating physician at regular intervals for clinical evaluation of efficacy, investigations with regard to safety, and recording of ongoing medication. Data from 131 patients were available for intention to treat analysis at the end of the 2 year study.

Study sample during the followup period up to 5 years: At 2 years, the formal double blind part of the study ended. Some investigators did not wish to continue. As a consequence, 48 patients were lost to followup. Furthermore, 8 patients died. No relationship to the underlying disease or treatment was suspected in any case. Thus, the material available for statistical analysis consisted of data from 75 patients, 40 in Group E, originally taking auranofin, and 35 in Group D, originally taking placebo.

From 2 to 5 years the patients were treated openly, guided by clinical disease activity and at the discretion of the treating physician. Various NSAID were given. Annual assessments were made of clinical variables — number of swollen joints, Ritchie articular index[7], duration of morning stiffness, grip strength, and general health measured by 100 mm visual analog scale (VAS) — and of outcome measures — pain (100 mm VAS), Stanford health assessment disability index (HAQ)[8], Keitel functional index[9,10], and Beck depression inventory scale[11].

Radiographs of hands, wrists, and feet were obtained once a year. Radiographic evaluation was done by one radiologist (HP), who was blinded to the treatment the patient received. Larsen score[12], erosion score (score of joints with Larsen score 2 or more), number of engaged joints (number of joints with Larsen score 1 or more), and number of eroded joints (number of joints with Larsen score 2 or more) were determined.

Statistical analysis. Changes over time (area under curve, AUC) were calculated for each variable, and the median changes in AUC between the 2 treatment groups were compared. The Wilcoxon signed rank test for paired data was employed to evaluate changes within treatment groups over time, and the Mann-Whitney 2 sample test was used to evaluate differences between the groups.

Radiological progression was estimated for each patient by calculating a trend over the 6 occasions of radiographic evaluation. Such a calculation

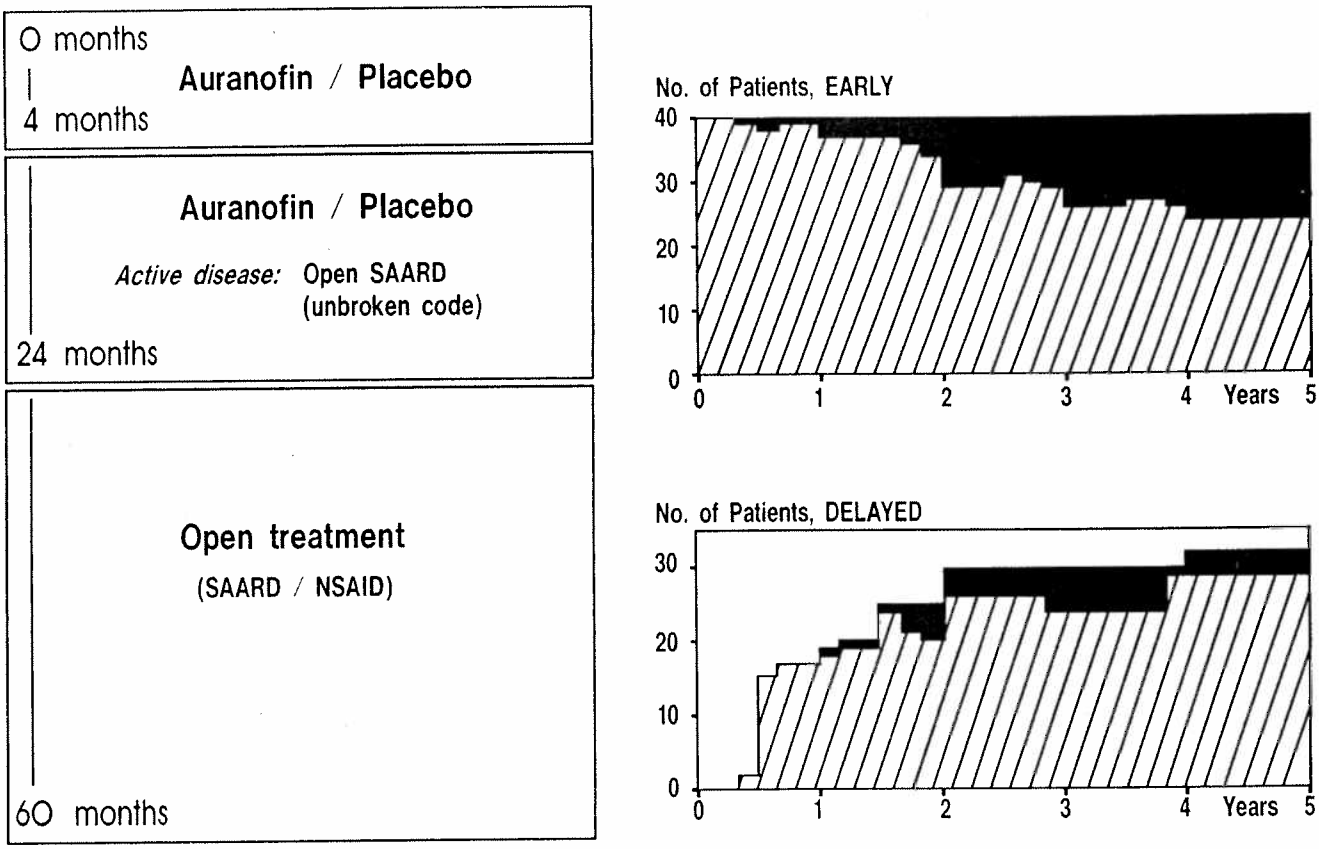

Fig. 1. (Left) Schematic of the treatment schedule during the 5 year study. (Right) Cumulative SAARD therapy over 5 years in patients receiving early auranofin therapy (n = 40) and delayed SAARD therapy (n = 35). placebo/NSAID, SAARD therapy, stopped SAARD.

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gives a rough estimate of changes over time, and a systematic difference reflects a different development in the progression curve for the 2 treatment groups. The Mann-Whitney test was applied for this comparison.

A systematic difference between treatment groups, or a systematic change over time within treatment groups, was considered at $p < 5\%$. Unless otherwise stated, results are presented as median (range).

RESULTS

Table 1 shows the demographic data and baseline variables for the 75 patients available for statistical analysis at 5 years. The principal baseline data of the 56 patients not followed for 5 years, shown in Table 2, were essentially similar, verifying that our study sample was still representative.

The E group and the D group followed for 5 years were comparable with regard to demographic data and variables recorded at baseline, and also at the 2 year analysis. The 75 patients followed for 5 years differed from the 56 patients lost between 2 and 5 years with regard to the variables presented in Tables 1 and 2 in only one respect. Larsen score at 2 years was higher in the D group followed for 5 years than in the D group lost to followup: 27 (0–88) versus 18 (0–39).

Duration of SAARD therapy was 48 (6–60) months in the E group and 42 (0–56) months in the D group. The number of different SAARD prescribed for each patient in the E group ranged from 1 to 6, median 1, and in the D group from 0 to 7, median 2. Delay to SAARD therapy was 12 (4–60) months (mean 8 months) in the D group. After 5 years, 16 patients in the E group were treated with NSAID only, and 24 were taking SAARD. In group D, the corresponding numbers were 3 and 29. Three patients avoided SAARD treatment altogether. In the E group, auranofin was given for 24 (4–60) months, and 9 patients continued taking auranofin throughout the 5 year period. Details of SAARD therapy in the 2 groups are shown in Table 3.

Table 1. *Baseline characteristics of the 75 patients available for statistical analysis at 5 years. Early: early auranofin treatment (n = 40); Delayed: delayed SAARD therapy (n = 35). Values are median (range)*

	Early	Delayed
Female/male	21/19	19/16
Age (yrs)	58 (28–73)	55 (26–78)
Disease duration (mo)	10 (2–24)	9 (3–24)
RF (titer)	20 (0–2560)	80 (0–640)
RF (pos/neg)	33/7	19/16
Steinbrocker functional class (I/II/III)	9/29/2	12/21/2
Clinical measures		
Ritchie index (n)	12 (0–36)	15 (0–32)
No. swollen joints (n)	11 (0–38)	9 (1–31)
Morning stiffness (min)	90 (0–300)	120 (0–300)
Grip strength (mm Hg)	100 (25–300)	121 (29–300)
General health (mm, VAS)	39 (4–98)	43 (0–80)
Outcome measures		
Pain (mm, VAS)	44 (6–97)	51 (7–77)
HAQ (0–3)	0.6 (0–2.4)	0.6 (0–2.2)
Keitel (0–100)	32 (0–60)	27 (0–52)
Beck (0–3)	0.29 (0–1.1)	0.25 (0–1.1)
Radiology		
Larsen score (n)	6 (0–42)	10 (0–23)
Erosion score (n)	0 (0–33)	2 (0–19)
No. engaged joints (n)	5 (0–23)	8 (0–21)
No. eroded joints (n)	0 (0–14)	1 (0–8)

RF: rheumatoid factor.

Table 2. *Baseline characteristics of the 56 patients not available for statistical analysis at 5 years. Early: early auranofin treatment (n = 27); Delayed: delayed SAARD therapy (n = 29). Values are median (range)*

	Early	Delayed
Female/male	17/10	24/5
Age (yrs)	57 (24–73)	58 (19–74)
Disease duration (mo)	10 (4–24)	14 (2–24)
RF (titer)	80 (0–640)	20 (0–640)
RF (pos/neg)	20/7	20/9
Steinbrocker functional class (I/II/III)	5/20/2	10/17/2
Clinical measures		
Ritchie index (n)	12 (4–39)	14 (6–44)
No. swollen joints (n)	11 (2–32)	7 (3–26)
Morning stiffness (min)	75 (0–300)	90 (0–240)
Grip strength (mm Hg)	139 (27–300)	132 (23–300)
General health (mm, VAS)	50 (14–83)	52 (21–93)
Outcome measures		
Pain (mm, VAS)	48 (19–100)	54 (13–90)
HAQ (0–3)	0.8 (0–2.3)	0.6 (0–1.9)
Keitel (0–100)	31 (0–70)	23 (0–53)
Beck (0–3)	0.36 (0–1.0)	0.29 (0.07–0.9)
Radiology		
Larsen score (n)	6 (0–21)	8 (0–44)
Erosion score (n)	0 (0–13)	0 (0–40)
No. engaged joints (n)	6 (0–21)	7 (0–24)
No. eroded joints (n)	0 (0–4)	1 (0–20)

RF: rheumatoid factor.

Changes in clinical variables and in outcome variables over the 5 year observation period are shown in Figures 2 and 3. Significant improvement could be demonstrated during the followup period in all 5 clinical measures in the E group, whereas only the Ritchie articular index and duration of morning stiffness showed improvement in the D group. The improvement in the E group was significantly superior to the D group with regard to the number of swollen joints and the Ritchie articular index. A significant improvement was registered in all 4 outcome variables in the E group, but only in pain and in general health in the D group. Improvement was significantly superior in group E compared to group D with regard to the Keitel functional index and the Beck depression inventory scale.

The results of the radiological assessments are shown in Figure 4. At baseline, the degree of radiographic joint involvement was very similar in the 2 groups, with a slightly higher degree of destruction in the D group. An increase in the total number of erosions and the Larsen score was observed in both groups, but significant difference between

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Table 3. *Number of treatment months for each SAARD, and total number of SAARD treatment months, in patients receiving early auranofin treatment (n = 40) and those receiving delayed SAARD (n = 35). Values are median (range)*

	n	Early Median (range)	n	Delayed Median (range)
AF	40	24 (4–60)	5	12 (4–36)
D-Pen	10	14 (4–42)	24	12 (4–54)
HC	8	15 (4–30)	12	18 (6–54)
SS	6	6 (4–30)	7	12 (4–18)
MY	7	12 (4–30)	12	6 (4–52)
AZ	2	6 (6–6)	5	12 (10–28)
MTX	1	6 (6–6)	3	6 (6–18)
PR	1	6 (6–6)	3	12 (12–36)
No SAARD treatment	24	29 (0–54)	35	18 (4–60)
Total SAARD treatment months	40	48 (6–60)	32	42 (12–56)

AF: auranofin, D-Pen: D-penicillamine, HC: hydroxychloroquine, SS: sulfasalazine, MY: myocrysine, AZ: azathioprine, MTX: methotrexate, PR: proreside.

treatments in favor of the E group was already present after one year and was maintained throughout the whole period of observation. At 5 years, the Larsen score and the erosion score in the D group had reached values roughly twice those in the E group, $p = 0.004$ and $p < 0.002$, respectively. If the patients with early initial damage (Larsen score >12) were excluded from the statistical analysis, a significant difference between the 2 groups was still present after 5 years, $p < 0.01$.

The same pattern was seen in number of engaged joints and number of eroded joints, with significant differences between groups in favor of group E at 5 years, $p = 0.01$ and $p < 0.004$, respectively.

DISCUSSION

Our study constitutes a prospective 5 year followup of patients with early RA (disease duration less than 2 years). Two treatment regimens were compared, early SAARD (auranofin) treatment versus delayed 2nd line therapy. The results at 2 years, as published, demonstrated a significant difference between the 2 treatment alternatives in favor of the group receiving "early" treatment with regard to out-

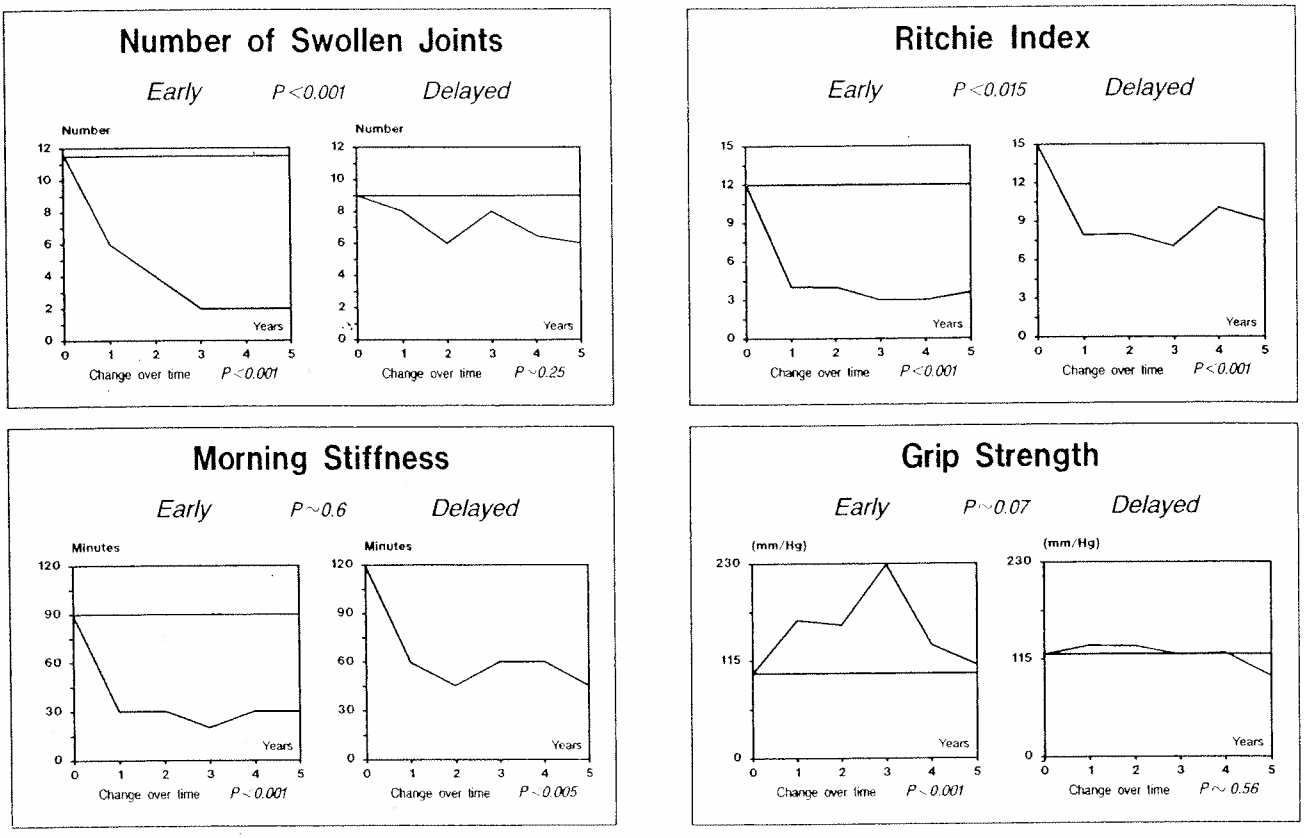

Fig. 2. Clinical measures over 5 years presented as AUC in patients receiving early auranofin (n = 40) and delayed SAARD therapy (n = 35). Median values are shown. p values are given for differences in AUC between groups, and changes over time within groups, for number of swollen joints (n), Ritchie articular index (n), duration of morning stiffness (min), and grip strength (mm Hg). Not shown: general health (differences between groups: $p = 0.2$; change over time Early: $p < 0.001$; change over time Delayed: $p > 0.01$).

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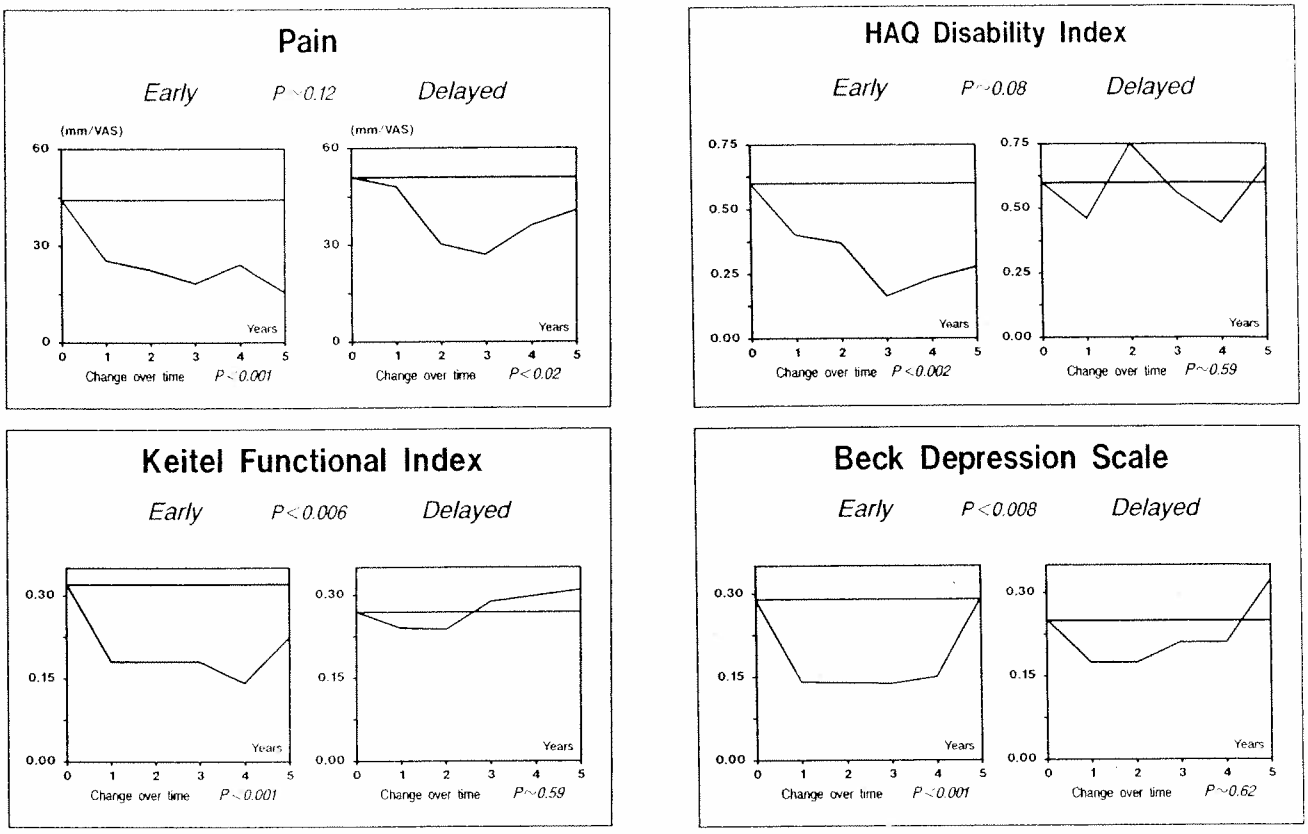

Fig. 3. Outcome measures over 5 years presented as AUC in patients receiving early auranofin (n = 40) and delayed SAARD therapy (n = 35). Median values are shown. p values are given for differences in AUC between groups, and changes over time within groups, for pain (mm, VAS), HAQ disability index, Keitel functional index, and Beck depression scale.

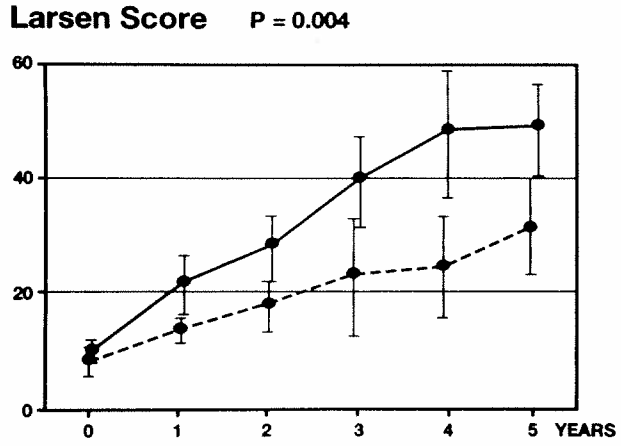

Fig. 4. Larsen score over 5 years in patients receiving early auranofin (n = 40) (broken line) and delayed SAARD therapy (n = 35) (solid line). Values are given as mean and 95% confidence limits.

come, including radiography[5]. After 3 additional years of followup, maintained or even increased improvement in clinical and outcome measures in the "early" group was found, and differences between groups in these measures consistently favored the "early" group. In accordance with these findings, progression of radiographic joint destruction was slowed in the "early" group, resulting in a difference in radiographic scores at 5 years of about 100%.

The patients available for final analysis made up only a part of those originally included in the double blind study. Patient loss was considered random, as whole centers dropped out after 2 years, and no selection bias was evident. Furthermore, the baseline characteristics of the patients followed for 5 years were similar to those lost after 2 years, indicating that the present subset was indeed representative of the original sample and not a selected subgroup.

The only difference between the E group and the D group was a mean time lapse of 8 months to start of SAARD therapy. How can this relatively short interval explain the pronounced differences still present after 5 years?

The earlier use of 2nd line drugs has been advocated on the premise that intervention before the formation of pannus and the onset of joint destruction should offer a better chance of reversing the inflammatory process and inducing remission[13]. As radiological joint erosions are a consequence of pannus, and as erosions are irreversible, the formation of pannus may be a point of no return where the

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process becomes self-perpetuating. This may explain why no drug has yet been shown to do more than slow the progression of radiological erosions. In the presence of existing erosions, progression is bound to continue despite medical treatment. At study entry, disease duration in the patients followed here was only about one year. Nevertheless, half the patients already presented joint erosions. The decline in progression rate after the first year of disease found by van der Heijde, *et al*[14] was not obvious in our study, but the progression rates in the E and D groups were markedly different.

An implication of these data may be a therapeutic window in the early course of RA, a window that exists only before the establishment of pannus and subsequent erosions. Such a therapeutic window has been suggested by Wolfe, *et al*[4] on the basis of a retrospective analysis of data from patients with RA followed for many years.

The manner in which drug therapy may influence the disease process in the proposed therapeutic window remains speculative. It may be related to the formation of pannus responsible for articular cartilage and bone destruction. Of the cytokines that have been identified in arthritic joints, interleukin-1 (IL-1) appears to be especially important, as it stimulates fibroblast-like synoviocytes to proliferate and to secrete metalloproteinases, prostaglandins, and cytokines[15]. In this respect, it may be relevant that auranofin has been shown to block the synthesis of IL-1[16].

Apart from the slowing of radiographic progression, process and outcome variables improved throughout the 5 year observation period in the E group, as shown in the AUC of each variable. This finding was in contrast to the D group, where only pain improved. Functional outcome reflected in the HAQ index showed a significant improvement in the E group, but not in the D group. The consistency of the results, with improvement in the E group in all the variables registered, and between-group differences always favoring E, gives confidence to our findings.

If further studies confirm our results, it will have important consequences for the treatment strategy of RA. Patients should seek medical advice as soon as symptoms appear, and active 2nd line therapy should be initiated as soon as the diagnosis has been established. If this could be achieved before irreversible tissue damage occurs, disease progression may be halted.

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